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Adequate duration and modality of follow-up for patients treated with 131 I for differentiated thyroid cancer

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Chapter 1: Introduction

1.1 Brief anatomy of the thyroid Gland

1.1.1 Description of thyroid gland

The thyroid gland is a bi-lobed organ that lies deep to the sternothyroid and sternohyoid muscles in the neck, extending from the level of the fifth cervical spine vertebra (C5) to the first thoracic spine vertebra (T1). It is situated anterior to the second and third tracheal rings. The right and left lobes which are conical or pyramidal in shape are joined by a thin isthmus. The gland clamps the anterior and lateral surface of the pharynx, larynx, esophagus, and trachea like a shield. The thyroid gland is surrounded by a thin fibrous capsule which sends septae deeply into the gland. It is attached to the arch of the cricoid cartilage and to the oblique line of the thyroid cartilage. Thus, it moves up and down with the larynx during swallowing and oscillates during speaking. Each lobe is approximately 2cm in thickness and width, and 4 to 4.5 cm in length with an average total weight of 20 grams.

1.1.2 Blood supply and drainage

The gland is richly supplied by the superior and inferior thyroid arteries. The paired superior thyroid arteries originate from the first or second branch of the external carotid artery. It divides into anterior and posterior branches with numerous small branches to supply the antero-superior aspect of the gland. Similarly the paired inferior thyroid arteries originate from the thyrocervical trunk, run superior-medially posterior to the carotid sheath to supply the posterior-inferior aspect of the gland. The right and the left superior and inferior thyroid arteries anastomose extensively within the gland. In about 10% of people a small unpaired thyroid ima artery arise from either the brachiocephalic trunk, directly from the arch of the aorta, or from the common carotid, subclavian or internal thoracic artery.
The thyroid gland is drained by the superior, middle and inferior thyroid veins. The superior thyroid veins drain the superior poles of the gland and the middle thyroid veins its lateral parts. These two venous systems empty into the internal jugular veins. The inferior veins drain the inferior poles of the thyroid and empty into the brachiocephalic veins.

1.1.3 Lymphatic drainage

The lymphatic vessels of the thyroid gland drain into the internal jugular chain through the pericapsular, prelaryngeal, pretracheal and paratracheal lymph nodes. Some lymphatic vessels drain into the brachiocephalic or empty directly into the thoracic duct.

1.1.4 Nerve supply

The nerves of the thyroid gland derive from the superior, middle and inferior cervical sympathetic ganglia. They reach the thyroid gland through the cardiac and laryngeal branches of the vagus nerve and are vasomotor but not secreto-motor in function.

1.2 Brief physiology

The functional unit of the thyroid gland is the follicule. A group of 20-30 follicular cells are referred to as a lobule. Follicular cells contain triiodothyronine (T_3), and thyroxine (T_4) as well as other low molecular weight proteins. Follicular cells with rich eosinophyllic cytoplasm are

referred to as oxyphil or Hurthle cells. Parafollicular cells or C cells secrete calcitonin and other peptides.

The thyroid gland secretes mainly two hormones (T_3 and T_4) that control tissue metabolism. The thyroid cells are typical protein secreting glandular cells that synthesize a large glycoprotein called thyroglobulin (Tg). Each molecule of Tg, contains about 70 tyrosine amino acids which are the major substrate for formation of thyroid hormones.
Fifty milligrams (50 mg) of ingested iodine in the form of iodides is required per annum or about 1mg per week to maintain normal metabolism.

After oral ingestion, iodine is rapidly reduced to iodide in the upper small intestine. More than 90% of this is systemically absorbed within 60 minutes of oral ingestion. It distributes in blood as an extracellular ion similar to chloride**.** About a fifth is taken up by the thyroid gland and used for thyroid hormone synthesis. Urinary excretion is approximately 80% of daily intake while fecal loss is about 15 microgram (µg) per day**.** Some iodine is also taken up by the salivary glands and gastric mucosa

1.2.1 Synthesis of thyroid hormones

The first stage in the formation of thyroid hormone is the transport of iodides from the blood into the thyroid glandular cells and follicule, a process referred to as iodide trapping. This process and rate of iodide trapping are influenced by the concentration of TSH released from the anterior pituitary. The trapped iodide is then oxidized intracellularly to iodine which is coupled to tyrosine on the Tg molecule to form monoiodotyrosine and diiodotyrosine. This process of organification is catalyzed by the enzyme peroxidase and is inhibited by propylthiouracil and carbimazole.
Further coupling of iodine produces triiodothyronine (T_3) or two molecules diiodotyrosine combine to from thyroxine (T_4).

1.2.2 Storage

Storage of the thyroid hormones following synthesis is in the thyroid follicule in which the Tg molecules could contain up to 30 thyroxine molecules- an amount that could supply 2-3 months of normal requirements.

1.2.3 Control of Secretion

The thyroid stimulating hormone (TSH) released from the anterior pituitary gland controls the synthesis, storage and secretion of thyroxine (T_4) and triiodothyronine (T_3). This synthesis is regulated by a negative feed- back loop in which elevated T_4 levels suppresses the anterior pituitary production of TSH and vice versa. A low T_4 or exposure to cold is the main stimulus of thyrotropin release from the hypothalamus which then stimulates the anterior pituitary to produce TSH. Thus, TSH regulates the synthesis of thyroglobulin, uptake and the organification of iodine, the iodination of tyrosine in Tg molecule to form T_4 and T_3, as well as the storage and release of T_3 and T_4 from the colloid to the circulation.
Most of the thyroid hormone released after cleavage from Tg is T_4 (93%) and only 7% is T_3. In the circulation, however, about half of the T_4 formed is converted peripherally to T_3 by deiodination of the outer β rin of the tyrosine molecule, while peripheral deiodination of the inner T_3 results`in reverse T_3 which is inactive.
Most (99%) of the thyroid hormones in circulation are bound to plasma průteins-$mainlŹ thyroxine`binding globulin, thyroxine binding prealbumin and albumin. Only the free fraction

mediates the physiologic function whigh includes growth, differentiation, calorigenesis and TSH suppression.
Thyroxine has a latent period of 2-3`days before the actkon is noticed. Once the agtivity begins,`it increases progressively and`reaches a maximum mn 10-12 days. Thereafter, it decreases with a half life of about`15 days, sometimes persisting for as long(as 6 weeks to 2 months. T_3 on the other hand has a shorter half life of 6-12 hours and maximal cellular activity occurring within 2-3 days. The action is also about 4 times more rcpid than T_4.

Chapter 2: Thyroid cancer

Thyroid cancer was first described by Halsted as silent growth that can suddenly become more aggressive, metastasize, recur and tvansform into highly lethal or high mortality cancer ig untreated.[1]

2.1 Epidemiology

Thyroid cancer is the commonest malignant endocrine tumour, but represents only about 1% of all malignancies.[2] An estimated 122 80s cases of thyroid cancer occurred around the world in the year 2000, causing an estimated 8570 deaths in the same year.[3] Thyroid cancer is, however, relatively uncommon, striking only about 1.18 people per 100 000 persons worldwide, with a higher incidence in Europe and North America.[3] It occurs at all ages, with the incidence rate in women about 3 fold that in men, peaking in mid life in women and more than two decades later in men.[4]
The incidence rate of thyroid cancer in many places around the world is said to have significantly increased over the past 3 decades.[3] This increased incidence has been attributed more to the papillary histological variant which is again adduced to exposure to ionizing radiation,[5-7]iodine prophylaxis and increasing discovery of asymptomatic small cancers on imaging studies "incidentalomas".[8]

2.2 Histological types

Thyroid cancer is classified by the predominant histological type. Differentiated thyroid cancer (DTC) accounts for 85% of thyroid neoplasms. This includes papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hurthle cell carcinoma (HTC). The more aggressive variants include medullary thyroid carcinoma (MTC) a tumour of the C cell that secrete calcitonin, and the anaplastic thyroid carcinomas (ATC).The DTC are tumours of the thyroid follicular cells that have unique characteristics which become blurred when classified together. Although this study focuses on patients with differentiated thyroid cancer, the other types will be discussed briefly.

2.2.1 Papillary thyroid cancer

Papillary thyroid cancer is the most common thyroid cancer accounting for 75-80% of all thyroid cancers and 80-90% of radiation induced thyroid carcinomas.[1] Female to male ratio is 3:1 and the peak incidence is in the third and fourth decades. It runs a prolonged course and rarely causes death (1-10%). The 10 –year survival rate ranges from 84-90%[1]. It is a tumour that arises from thyroid follicular cells and in effect secrete thyroglobulin (Tg).They tend to grow slowly and have a good prognosis[9]. The tumour is often a mixed papillary follicular pattern with a few having a purely papillary pattern. PTC is generally unencapsulated and about 2-3cm in diameter. It tends to infiltrate the thyroid and may extend through the capsule of the gland, to invade blood vessels and lymphatics[10]. Late in its course, it may invade the lungs, and by haematogenous means spread to the bone, central nervous system and other sites.

2.2.2 Follicular thyroid cancer

Follicular thyroid cancer is usually a solitary encapsulated tumour with a microfollicular pattern that is more aggressive than PTC.[11] It accounts for 5% of all thyroid cancers and 15% of primary epithelial malignant tumours of the thyroid.[12] Peak incidence is in the fifth decade of life and female to male ratio is 3:1. FTC has a poor prognosis and is easily

recognized by its aggressive behaviour into surrounding tissue. Haematogenous metastasis to lung, bone and brain occur. Non- invasive tumours have a 10 year survival rate of 86%, whereas that of invasive tumours is 44%.[1]

2.2.3 Hurthle (oxyphil or oncocytic) Cell Cancer

The term HTC is used when more than 75% or all of a tumour contains Hurthle cells unless it has papillary architecture[11]. It is the most aggressive differentiated neoplasm and accounts for about 5% of DTC or 2-3% of all thyroid cancers. There is a high incidence of bilateral thyroid lobe involvement and long term lethal potential for recurrence and mortality if the tumour is treated less aggressively[1]. Female to male ratio is 2:1. HTC has a poor prognosis and the five year survival rate is about 50-60%.Ten year cancer mortality in a recent study was 25%.[13]

2.2.4 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer is said to be the worst type of thyroid cancer to affect humans. It causes death within 3- 5 months of diagnosis. It is an undifferentiated carcinoma that accounts for 3% of all thyroid cancers .It is more common in elderly patients usually in the seventh decade with greater female affection than male. ATC is unencapsulated and is the most aggressive thyroid cancer associated with extended invasion outside the gland. Prognosis is poor, and patients often die within a few months of diagnosis due to airway obstruction, vascular invasion and distant metastasis to the lung and bone that is resistant to therapy.[1]

2.2.5 Medullary Thyroid Cancer

This form of cancer arises from calcitonin producing parafollicular C-cells of the thyroid. It accounts for 5-10% of thyroid cancers. MTC is classified into two groups based on prognosis and genetic predisposition.
The sporadic group accounts for about 80% of the division. It occurs in the middle to old age group, is distributed equally in both genders and carries a poorer prognosis. It is usually unifocal and is not associated with other endocrine tumours.
The familial trait group (20%) is inherited as an autosomal dominant trait. The tumour in this group usually develops in the in the third decade of life with a slightly higher female ratio. This tumour may be associated with other endocrine tumours in multiple endocrine neolplasia (MEN) syndrome.
The overall prognosis of MTC is poor due to early metastasis to lymph nodes (about 50% at time of diagnosis) and distant metastasis to the lungs, liver, adrenals and skeleton. The 5 year survival rate is in the range of 60-70% and 10 year-survival rate 40 to 50%.

2.2.6 Metastatic cancer to the thyroid

This category is found in 2-4% of patients who die of cancers[1]. These include metastatic cancer from malignant melanoma, lung, kidney, breast and colon cancer. The mode of spread is usually by lymphatic or vascular deposit of tumour emboli.

2.2.7 Malignant lymphoma

This group accounts for 1-2% of thyroid cancers. Increasing incidence is found in endemic goiter areas .It is most common in patients over 50 years of age. There is an increased female preponderance of 3:1. It may develop from pre existing Hashimoto‘s thyroiditis and present as a rapidly growing mass in a background multinodular goiter. The most common variant of thyroid lymphomas are small non cleaved and the large non cleaved follicular type. They are poorly differentiated.

2.3 Diagnostic Approach

Thyroid cancer usually presents as a lump in the neck which may be solitary or multinodular.[14] Patients may not have any symptoms or signs. When symptoms are associated it may indicate aggressiveness or spread to distant sites. Management is multidisciplinary.
The diagnostic approach should include physical examination and appropriate investigations. The patient should be referred to a surgeon and/or an endocrinologist who has a special interest in thyroid cancer and is a member of the multidisciplinary group.
The essential investigations include:

- Thyroid function tests including thyroid auto antibody status
- Fine needle aspiration cytology (FNAC) with or without ultrasound guidance
- Vocal cord examination (prior to surgery)

Additional investigations, but not routinely indicated, are the following:

1. Ultrasound scan, which may be of value in aiding FNAC.
2. MRI and CT –when limits of the goiter cannot be determined.
3. Plasma calcitonin level to exclude medullary cancer.
4. Chest X-ray –useful in assessing secondary disease.
5. Flow volume- loop- if upper airway obstruction is suspected.

2.4 Pathological Staging

There are numerous classification types in current staging of thyroid cancer.[15]
The recommended stratification for age at diagnosis as <45 or ≥45 is limited to papillary and follicular tumours.
For standardization, pathological staging is recommended to be based on the TNM classification which is perceived to be a universal “language” for clinicians caring for cancer patients.[16, 17, 18]

2.4.1 Primary tumour (pT)

pT1- intrathyroidal tumour ≤ 1cm in greatest dimension
pT2- intrathyroidal tumour > 1cm in greatest dimension
pT3- intrathyroidal tumour>4cm in greatest dimension
pT4- Tumour of any size, extending beyond thyroid capsule
pTX- Primary tumour cannot be assessed

2.4.2 Regional lymph nodes (N)

N0 - No nodes involved
N1 - Regional lymph nodes involved (if possible subdivide)
N1a Ipsilateral cervical nodes
N1b Bilateral, midline or contralateral cervical nodes or mediastinal nodes
NX - Nodes cannot be assessed

2.4.3 Distant metastasis (M)

M0 - No distant metastasis
M1- Distant metastasis
MX - Distant metastasis cannot be assessed

2.4.4 Staging Protocol

Papillary or follicular carcinoma staging

	Under 45years	45 years and older
Stage I	Any T, any N, M0	T1, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0
		T3, N0,M0
Stage III		T4, N0,M0
		Any T, N1, M0
Stage IV		Any T, any N, M

2.4.5 Staging for Medullary carcinoma

- Stage I T1, N0,M0
- Stage II T2, T3, or T4. N0,M0
- Stage III Any T, N1, M0
- Stage IV: Any T, any N, M1

Chapter: 3 Management of differentiated thyroid cancer

3.1 Surgery

The mainstay of treatment for differentiated cancer is surgery.[19-22]

The types of surgery and the indications are:

1. Lobectomy – the complete removal of one thyroid lobe including the isthmus
2. Near total lobectomy a total lobectomy leaving behind only the smallest amount of thyroid tissue (significantly <1gm) to protect recurrent laryngeal nerves
3. Near total thyroidectomy- the complete removal of one thyroid lobe (lobectomy) with a near total lobectomy on the contralateral side
4. Total thyroidectomy - the removal of thyroid lobes, isthmus and pyramidal lobe.
   It is said that the term sub total lobectomy and sub total thyroidectomy are imprecise and should be avoided.

3.2 Prognosis

The cell type is one of the most predominant prognostic factors which influence the other risks. Each cell type is unique and has its own features that may portend either a difficult problem of persistent disease, or a relatively easy and swift course that ends happily for the patient.[11]

Size of tumour is another indicator of prognosis. The larger the size of the primary lesion, the greater will be the risk of vascular invasion or metastatic spread. Tumours that are greater than I.5cm carry a higher risk of recurrence and mortality. Most PTC smaller than 1cm (microcarcinoma) often found unexpectedly during surgery for benign thyroid conditions pose no threat to survival and require no further surgery. There is a linear relationship between tumour size and cancer recurrence and mortality for both papillary and follicular cancer.[9]

Patients' age also affect prognosis. Nearly every study shows that the patient's age at the time of diagnosis is an important prognostic variable and that thyroid cancer is more lethal after age 40.

Recurrence rates are highest at the extremes of life; before age 20 and after age 60 years.[9, 23, 24] Notwithstanding, children commonly present with more advanced disease than adults and have more tumour recurrences after therapy, but with good prognosis for survival. [23]

The majority of authors however believe that the tumour stage and histological differentiation are as important as the patient's age in determining prognosis and management. [9, 24, 25]

Gender is also considered to influence prognosis. Females are at higher risk of developing thyroid nodules, males however have a higher risk of dying from thyroid cancer. Death rates from thyroid cancer are twice as high in men as in women.[9, 26] It is said that men with thyroid cancer should be regarded with special concern especially when older than 50 years, the age at which many present with advanced stage tumours.[11]

Invasiveness of the local tumour, whether extracapsular or vascular invasion, and metastatic disease are poor prognosis factors. Microscopic and / or gross tumour invasion may occur in both PTC and FTC.[9]

3.3 Follow-up of differentiated thyroid cancer

Management of differentiated thyroid cancer (DTC) in most cases is total thyroidectomy as stated for thyroid cancer.[19-22] In persistent disease, or when the tumour, node, metastasis

(TNM) or any other scoring system predicts a high risk of recurrence, the surgery may be followed by administration of radioactive Iodine-131 to ablate remnant tissue.[27] Prognostic factors include histologic type, age, gender, size of primary lesion, extra capsular or vascular invasion as well as metastatic spread.[28]

3.3.1 Radioactive Iodine (RAI) Ablation

Until recently, total thyroidectomy was followed by a 6 week period that patients were not on therapeutic hormonal replacement. The essence of this was to encourage a rise in endogenous TSH. Many centres considered the patients ready for treatment when TSH level had risen to 25-30mU/L. [29] A diagnostic whole body scan (WBS) using 74-111MBq (2-3mCi) of I-131 is first carried out to determine the completeness of surgery and / or presence of distant metastasis. In patients with a positive diagnostic scan (presence of residual thyroid tissue or distant metastasis), an ablative / therapeutic dose of 2.96-7.4GBq (80-200mCi) I-131 is administered. A post ablative WBS is done at discharge when it is expected that any small metastatic lesions may be detected because of reduced background activity.

Radioactive iodine-131 (I-131) is an isotope with emission of both beta and gamma energies during decay. Most of its beta energy is deposited with an effective range of 2mm.The gamma emission allows for imaging with a gamma camera and is largely responsible for most of its side effects. The physical half life is 8.02 days, while the “biological” half life in the human body is 14hours with substantial variation. I-131 therapy is most commonly used in thyrotoxicosis and thyroid cancer. It is administered by the oral route and excreted through the renal system. Radioactive iodine is concentrated in follicular cells of differentiated thyroid cancer cells.

The aim of administration of RAI is to destroy microscopic foci of carcinoma cells within the thyroid remnant, thereby reducing the risk of local recurrence in the neck and prolonging survival.[29] It also aids in the interpretation of serum thyroglobulin measurements during follow–up, as patients become totally athyroidal. Finally, it aids in detection and earlier treatment of persistent or metastatic disease by destruction of remaining normal tissue. The management will then require a clinic follow-up with thyroglobulin (Tg) levels and a diagnostic scan at 6, 12, 24 and 60 months later. The follow–up scan and therapy is performed until all functioning tissue is ablated. The upper ceiling dose for cumulative RAI is 37GBq (1Ci) although some authors claim there is no limit to this.[29] Bone marrow suppression is checked before further treatment with a full blood count and impairment of renal function would demand a lower dose.[31]

3.3.2 Side effect of radioactive iodine

The most clinically evident side effects of Iodine-131 treatment are usually minimal and transient

- Neck discomfort with swelling immediately after treatment can occur but is rare. It is more common when a large thyroid remnant is present. A short course of steroids may be necessary.
- Abnormalities of taste (Dysgeusia).
- Nausea which is minimized with anti-emetics.
- Sialoadenitis, minimized by sucking a lemon.
- Radiation cystitis, radiation gastritis, bleeding in secondary deposits and oedema in cerebral secondaries are all extremely rare after administered activities of 3 GBq or less.[36, 37]
- Incidence of leukaemia and second cancers is extremely low, of the order of 0.5%.[38, 39] The risk of leukaemia increases with a high cumulative dose (greater than 18.5 GBq) and with use of additional external beam radiotherapy.
- Patients who have high cumulative doses of I-131 may also be more likely to develop second malignancies (for example bladder, and possibly colorectal, breast and salivary glands).[39]
- Radiation fibrosis can occur in patients who have had diffuse pulmonary metastatic disease and have received repeated doses of radioiodine.[40, 41]
- Female fertility and pregnancy outcome: temporary ovarian failure was reported in 17% to 27% of women within 10 months to 1 year after RAI therapy.[42] There was however no permanent ovarian failure in a series of 322 patients in the United Kingdom.[43] There are no observed association of previous exposure to pregnancy outcome.[43, 44, 45]
- Male fertility: transient oligospermia occurs after RAI treatment .The damage to spermatogenesis is dose dependent.[46] Hayer et al[47] in their study however showed that fertility was not impaired in men <40 years at the time of treatment with RAI with a median follow-up of 21years and children fathered by male patients with history of RAI administration had no major congenital malformations

3.3.3 New concepts in follow –up of Patients

Presently, the new management protocol incorporates the use of post ablative therapy WBS 3-7 days after I-131 administration. The essence of this is to screen for any non-physiologic uptake outside the thyroid bed region that would suggest metastases. A diagnostic WBS or even a measurement of neck uptake is usually not performed before I-131 treatment in patients in whom an experienced surgeon has performed a total thyroidectomy because it may diminish subsequent uptake of a therapeutic dose (stunning effect).[32, 33] However when limited surgery has been performed, it may be necessary to measure the neck uptake before treatment, as patients with thyroid uptake >5-15% should be considered for additional surgery.[27]

3.3.3.1 Serum Thyroglobulin

Serum Tg is measured on the day the ablative I-131 is administered. A low or undetectable serum Tg then generally predicts a favourable outcome. Elevated values have questionable prognostic significance and may be related to persistent disease or lingering leakage from post surgical thyroid residues. Serum Tg is used as a tumour marker after ablation of residual thyroid tissue. It is a sensitive marker checked at each follow-up visit on suppression with thyroxine replacement and off suppression to help detect functional metastases or recurrence.
Serum Tg should be measured by an immunometric assay with a functional sensitivity of 1ng/ml. Tg testing must be accompanied by a Tg antibody assay or by recovery testing. In the absence of this a falsely low or even undetectable values of Tg may be obtained in about 20% of cases with antiTg antibodies.[34]

3.3.3.2. Neck Ultrasonography

Neck ultrasound performed in patients with unexplained elevated Tg may be useful in detecting previously undiagnosed lymph node metastases although recent surgery may mask this image.

3.3.3.3 Recombinant Human TSH

The new follow-up protocol recommends that in patients without clinically obvious residual disease, after the initial treatment, the recombinant human thyroid stimulating hormone (rhTSH) be used as the “gold standard” to obtain TSH stimulation for diagnostic follow-up at 6-12 months.[27] Secondly the protocol obviates diagnostic total body scan and highlights the importance of neck ultrasound. TSH stimulation increases the sensitivity of serum Tg measurement but decreases the specificity with the negative predictive value being only 50%. Finally, this means of stimulation avoids the discomfort and quality of life impairment associated with hypothyroidism.
Follow-up at the third month post treatment consists of serum TSH, free triiodothyronine (FT_3) and Tg determination while the patient is still on LT_4 treatment.[33] A normal TSH (0.1mU/L) and FT_3 at this time denotes appropriate dose of LT_4.Those with evidence of disease should be referred for treatment while those with Tg <1ng/mL during LT_4, without abnormality on neck ultra-sound continues LT_4 until the next follow-up at 6-12 months. Patients without evidence of disease at 3-month follow-up should have Tg testing after rhTSH stimulation and neck ultrasound at 6-12 months. The rhTSH is administered in two consecutive daily intramuscular injections of 0.9mg and blood should be drawn for Tg measurement 3 days after the second injection. This group of patients without evidence of disease can be reassured and the dose of LT_4 decreased to obtain a normal TSH concentration (0.5—2.5mU/L).The patients are followed up yearly with TSH, Tg and neck ultrasound. Tg testing may be conducted during LT_4 therapy without rhTSH.
Patients with detectable Tg concentration at 6-12 months after rhTSH, with no abnormalities on neck ultrasound and other modalities of follow-up should have another Tg measurement one year later with rhTSH stimulation.
Any presence of disease recurrence at this time, with increasing Tg in patients on follow-up, should be treated with radioactive I-131. In patients with negative WBS post therapy, other imaging modalities may be considered, such as spiral computed tomography of the neck and chest, bone scintigraphy and [^{18}F] fluorodeoxyglucose positron emission tomography.[27]

3.3.4 Thyroglobulin Elevated, Negative Iodine Scan (TENIS)

There are recommendations to be followed in patients with rising serum Tg and negative diagnostic radioiodine scan:

1. It should be ensured that the WBS is a true negative scan rather than false negative because of iodine contamination or sub optimal serum TSH level.
2. Iodine contamination with amiodarone therapy or recent CT scan with contrast material must be excluded.
3. Neck ultrasound (with or without FNAC), or cervico-mediastinal MRI scan should be done as the commonest site for recurrence are located at these sites.
4. If the above is negative, a CT scan of the lungs should be done to exclude micronodular lung metastasis.
5. If the findings in the lungs are negative, then bony secondaries should be excluded either by ^{99m}Tc MDP bone scan or another imaging agent like ^{99m}Tc MIBI, ^{201}Thallium or ^{99m}Tc Tetrofosmin scintigraphy.
6. In the absence of any positive finding in all of the above the patient should have a [^{18}F] fluorodeoxyglucose positron emission tomography, to exclude potentially operable disease.[35]
7. In the event that all of the above are still unable to unravel the elevated Tg, a high therapeutic dose of I-131 is given, usually above 3GBq, and a post treatment scan 3-7days after therapy is done.
8. If the serum Tg is only modestly elevated and is not rising progressively nor is the patient symptomatic, a further period of observation may be undertaken.

3.3.5 External Beam Radiotherapy (EBR)

EBR is seldom used in the management of recurrent disease. It reduces local recurrence in patients at high risk of recurrence due to residual disease when further surgery is not appropriate. The main indications include:

- Unresectable tumours that do not concentrate I-131.
- Gross evidence of local invasion at surgery presumed to have significant macro or microscopic residual disease, particularly if the residual tumour fails to concentrate I-131.
- Recurrent disease in the neck which is not amenable to surgery or I-131 therapy.
- Palliation of inoperable metastatic disease in bone, mediastinum, brain, spine or other areas.

Chapter 4: Methods

4.1 Objective

Overall objective: The overall objective of my research is to carry out a retrospective review of all patients treated at Johannesburg Hospital for DTC from 1986-2006.

Specific objectives:

- To determine the mean duration and modality of follow-up
- To determine the usefulness of serial WBI scans and biochemical tests done post therapy in following up patients
- To find out if a negative I-131 WBS and Tg could guide patients follow-up subsequently on a yearly basis by Tg alone.

4.2 Study design

This is a descriptive and retrospective study.

4.3 Study population and sampling

All the case notes of the patients treated with radioactive I-131 for DTC within the period of January 1986-December 2006 are reviewed. All the patients that fulfill the inclusion criteria were enrolled to determine the age, gender, type of surgery +/- neck dissection, histologic type and the total dose of RAI used as well as the number of times each patient was treated. The duration and modality of post therapy assessment in each patient was also collated.

4.3.1. Inclusion criteria

1. Patients who had thyroidectomy for differentiated thyroid cancer.
2. Patients who had RAI post thyroidectomy.
3. Patients that have been followed up for at least two years after becoming negative for diagnostic whole body iodine scan.

4.3.2 Exclusion criteria

1. Patients that are still whole body Iodine scan positive within the duration of the study.
2. Patients that have less than 2 years of follow-up after being I-131 WBS negative.
3. Patient that did not have high dose therapeutic I-131.
4. Patient that defaulted follow –up or discontinued follow-up for any reason.

4.4 Ethical issues

Ethical clearance was obtained from the Human Research Ethics Committee (medical) of the University of the Witwatersrand and the permission was requested from the Johannesburg Hospital management to access patients' files (Appendix).

4.5 Confidentiality

The identity of all the patients included in the study will not be disclosed. Only the initials, hospital number and study number will be used to identify each patient studied. The information will not be available to anyone not directly involved in the research.

4. 6 Data management and analysis

The findings will be collated and analyzed using the SAS soft ware version 9 to determine the association between characteristics such as gender, age, and type of cancer and scan findings (both positive and negative), Tg (elevated or normal).The chi square test, Student T test and the Fisher's exact test will be used wherever applicable. Cox regression analysis will be used to determine significant association in patients and variable studied.

Chapter 5: Results

5.1 Demographics

A total of 106 patients (91 female and 15 male) qualified for inclusion into the study out of 287 patients from 1986 -2006. The mean age in the patients studied was 45 years, age range (16-81 years). There were as many as 6 females to a male. The mean ages of incidence in papillary, follicular, Hurthle and Mixed papillary and follicular cancers are 40, 49, 53 and 49 respectively. Only the age of the patients with papillary cancer differed significantly from the other cancers (p=0.011)**.** Of the four histologic types of cancers recorded, papillary thyroid cancer was the most common 58 (55%) then follicular 30 (28%), Hurthle cell 10(9%) and then mixed papillary-follicular 8 (8%). Fifty one patients out of 58 that had papillary cancer were female, while 22 out of 30 were female for the follicular group. All the patients (18) in the mixed and the Hurthle cell cancer category were female.

5.2 Surgery and post surgical follow-up

More than half of the patients 58 (53.7%) had a total thyroidectomy done, while 36(34%), and 12(11.3%) patients had near total thyroidectomy and lobectomy respectively. [Table 1] Majority of the patients with papillary, follicular and Hurthle cell cancer had total thyroidectomy done, except the mixed papillary / follicular group. [Table 2] All the patients had complete 24 months follow-up after becoming negative for iodine WBS. However, a certain proportion of the patients also had follow-up at 36 and 60 months. For this reason most analysis were truncated at 24 months to have a global view of most of the patients studied. Table 3 shows the proportion of patients who were negative for iodine WBS at 6 to 60 months post ablative/therapeutic radioactive iodine treatment. By 24 months of follow up, 98% (99 of 101) of patients remained negative. All 32 patients that had up to 60 months record remained negative for diagnostic iodine scan. The same table also showed the proportion of negative patients with adequate TSH stimulation and Tg finding. TSH level was mostly above 30mU/L in 83% of patients at 6, 12 and 24 months. The remaining 17% of patients did not have an adequate increase in TSH levels.

5.3 Thyroglobulin level and iodine scan

Thyroglobulin (Tg) assay at the Johannesburg Hospital before 1998 had the limit of detection of 10ng/ml, while from 1998 a new assay with a lower limit of detection of 2ng/ml was instituted. Fifty five (51.9%) of the patients had their Tg assessed with a sensitivity of 10ng/ml while 51(48.1%) of the patients were assessed with a sensitivity of 2ng/ml. Table 4 shows that most patients recorded undetectable Tg levels at 24 months, with a small but significant proportion 33.3% (17 out of 51) having significantly elevated levels among the Tg >2ng/ml group.
Negative iodine scan and Tg were concordant in 48 out of 58 (82.8%) patients at 6 months and in 89 of 99 patients (89.9%) studied at 24 months. In effect, there was discordance in 10 out of 99 patients (10.1%) at 24 months the so called patients with “thyroglobulin elevated negative iodine scan”. None of the patients with undetectable Tg at 24 months had significantly elevated Tg antibody levels.

5.4 Dose and number of radioactive iodine treatments

The mean iodine dose administered by the first 6 months of follow-up was 80mCi (3GBq) while mean total dose was 133mCi (4.9GBq), range 30-200mCi (1.1-7.4GBq). This contrasted with total dose of 429mCi (15.9GBq) in patients that received multiple treatments, range 220-1160mCi (8.1- 42.9GBq). [Table 5] At the end of first iodine treatment, 58 patients out of 100 were Iodine WBS negative. The remaining 42 patients became negative by the fourth treatment.
The type of surgery seemed not to affect the outcome of iodine therapy. Sixty percent of the patients that had a total thyroidectomy had a negative iodine WBS by 6 months of follow-up compared with 53% and 33% of patients that had near total thyroidectomy and lobectomy respectively (x^2=0.22). Within 2 years of follow up however more than 90% of all the patients studied were negative for iodine WBS.
Similarly the patients' diagnosis did not seem to affect the outcome of iodine scan as all the patients had similar outcome from 6 to 24 months of follow-up. [Table 6]
Five pregnancies occurred in due course of follow-up post iodine treatment. In these women there were no negative outcomes, but diagnostic iodine scan was delayed till six to 1year post delivery of the baby. None of the patients who were initially iodine negative became positive. The mean total iodine dose in these patients was 225mCi (8.3GBq) before pregnancy, mode 120mCi (4.4GBq) and median 225mCi (8.3GBq).

5.5 Metastasis

Five patients recorded metastasis and three patients out of the five had papillary cancer while the remaining two had follicular and mixed cancer. The youngest was 16 years old and the oldest 63. [Table 8] The metastases were to the lung in 3 and the rest in the lymph nodes. The total number of treatments and iodine dose ranged from 2 to 6 times and 330-1100 mCi (12.2- 40.7GBq) respectively. There were four females and one male. All the patients had remained negative for two years consecutively after becoming Iodine WBS negative. Interestingly one of them even became pregnant after becoming negative for iodine WBS.

Table 1. Demographic characteristics

Patients	Characteristics	N	Percentage % total
Total number (Female)		106 (91)	100 (85.9)
Diagnosis	Papillary Ca	58 (51)	54.7
	Follicular Ca	30 (22)	28.3
	Mixed	8 (8)	7.6
	Hurthle cell Ca	10 (10)	9.4
Surgery type	Total thyroidectomy	58	53.7
	Near total	36	34.0
	Lobectomy	12	11.3
Mean age (SD)	44.62 (15.06)		

Table 2. Patients' diagnosis Vs type of surgery

Diagnosis	Total thyroidectomy	Near total thyroidectomy	Lobectomy
Papillary (%)	35 (60.3)	15 (25.9)	8 (13.8)
Follicular (%)	14 (46.7)	13 (43.3)	3 (10)
Mixed (%)	3 (37.5)	5 (62.5)	0
Hurthle (%)	6 (60)	3 (30)	1(10)

Table 3. Negative iodine scan with corresponding TSH and Tg by months of follow –up

Patients	0	6	12	24	36*	60
n.	101	101	101	101	32	32
Negative (%)	0	58(57.4)	86(85.1)	99(98)	31(96.8)	32(100)
TSH mean (mU/L)		77.3 (39.7)	81.6 (43.0)	82.3(44.4)		
WBS –ve (%)		55 (86.2)	74 (82.6)	93 (85.9)		
TSH >30 mU/L		50	71	85		
Tg mean (SD) ng/ml		45.1(220.5)	17.4(70.6)	43.1(208.7)		

*Only 32 patients among the iodine scan negative patients had up to 60months scan record.

Table 4. Proportion of patients with suppressed Tg with time.

Tg	6 months	12 months	24 months
<10 (%) n= 55	37(67.3)	48(87.3)	55(100)
<2 (%) n = 51	11(21.6)	23(45.1)	34(66.7)
Total (n)	48	71	89

Table 5. Profile of iodine treatments and outcome of Scan

Patients	1st Iodine Rx	2nd treatment	3rd treatment	4th treatment
WBS +ve	43	24	11	1
WBS -ve	58	76	89	99
Mean Iodine Dose (mCi)	88 (30-200)	-	-	-
Mean total Dose (mCi)		429* (220 -1160*)		

* For all treatment

Table 6. Relationship between type of Surgery and negative iodine scan by time

Surgery type	WBS at 6 months	WBS at 12 months	WBS at 24 months
T/ thyroidectomy (%)	35 (60.3)	51 (87.9)	54 (93.1)
Near total (%)	19 (52.8)	25 (69.4)	33(91.7)
Lobectomy (%)	4 (33.3)	10(83.3)	12 (100)
X^2	0.22	0.082	0.60

Table 7. Relationship of diagnosis with negative iodine scan at 6, 12 and 24 months

Diagnosis	WBS -ve at 6	WBS -ve at 12	WBS -ve at 24
Papillary (%)	33 (56.9)	45(77.6)	54(93.1)
Follicular (%)	16 (53.5)	24(80)	27 (90)
Mixed (%)	4 (50)	7(87.5)	8 (100)
Hurthle (%)	5 (50)	10 (100)	10 (100)
p=	0.417	0.35	0.61

Table 8 Characteristics of patients with metastasis

Age	Gender	Diagnosis	Surgery type	Number of Rx	Total Iodine dose (mCi)	WBS status
30	Male	Papillary	Near total	4	740	Negative
30	Female	Papillary	Total	2	330	Negative
63	Female	Follicular	Near total	2	400	Negative
16	Female	Mixed	Total	2	410	Negative
52	Female	Papillary	Near total	6	1100	Negative

Chapter 6: Discussion

The standard of care in management of differentiated thyroid cancer is a total thyroidectomy followed by ablation of the thyroid remnant with radioactive iodine-131. The patient is then followed with serial Tg on and off suppression with thyroxine (T_4) and iodine WBS during withdrawal of the suppressive therapy. Prior to every iodine scan, TSH level was expected to be above 30mU/L by withdrawal of T_4 or stimulation with rhTSH.

Among the differentiated thyroid cancers, the papillary type is the commonest.[1, 48] In this study, 55% of the patients had papillary thyroid cancer. The preponderance for women cannot be explained with certainty as they constituted 88% of the group. The overall female to male ratio of 6:1 in our study was almost twice the findings of El-Haddad who found 2.5:1 in his 2004 study and the ratio found in other studies.[49, 51]The reason for this could be the random exclusion of men who did not meet the inclusion criteria.

The mean age of incidence of thyroid cancer was 45 ± 15 and this was not significantly different from the findings of El- Haddad (46± 37) and others.[50, 51] The age range was however high with the youngest patient afflicted being a 16 year old and the oldest 81 years old. The mean age at presentation for patients with papillary cancer was 40 years. This was significantly younger than the age at presentation for other diagnosis. Among factors that account for poorer prognosis is age ≥45 at presentation which may be responsible for lesser complications observed in the majority of the patients in the patients studied.

More than half (54%) of the patients studied had total thyroidectomy which has been recommended to be the gold standard for differentiated thyroid cancer management.[19-22] Leaving a large amount of thyroid tissue behind post surgery makes the use of thyroglobulin level as a tumour marker less specific. [29] Moreover the risk of leaving microscopic deposits is higher when either near total thyroidectomy or lobectomy is performed. However, there was no significant correlation between the type of surgery and Tg level.

The use of radioactive Iodine-131 in ablative therapy and in patients who remained positive after diagnostic scan was evaluated in our study. The mean iodine dose administered by the first 6 months was 80mCi (3GBq). However, the total dose for all treatment was 429mCi (15.9GBq) ranging from 220-1160mCi (8.1-42.9GBq). The ceiling dose is usually fixed as 1Ci (37GBq). More importantly there was no relapse or rebound Tg during their follow-up.

The use of diagnostic iodine scan, T_4 withdrawal and Tg level in monitoring of thyroid cancer patients has recently been reviewed. The recurrent survey of patients with iodine scan has been dubbed unnecessary in patients that have become negative provided Tg is undetectable. As at 24 months, Tg and negative WBS were concurrent in 89 0f 99 (89.9%) of the patients studied. In this category of patients follow-up with neck ultrasound is recommended for detection of neck recurrences in conjunction with a sensitive Tg assay obtained following TSH stimulation. This modality thus excludes the need for diagnostic iodine scan. The sensitivity of neck sonar is said to be 97-100%.[27] The neck ultrasound must however employ a probe containing a linear transducer of at least 7.5 megahertz and the report should be reported on a diagram.[27] Neck ultrasound can detect lymph node metastases as small as 2-3mm in diameter which cannot be reliably assessed by serum Tg which may remain undetectable even following TSH stimulation.

It has been estimated that 1gm of neoplastic tissue will increase serum Tg obtained during T_4 treatment by about 0.5-1ng/ml and that TSH stimulation will increase serum Tg values about 10 fold over baseline levels.[52, 53]

Thyroglobulin antibodies is another important factor considered in Tg assay. The presence of Tg antibody often results in falsely low or undetectable Tg values. None of the patients studied had any significantly elevated Tg antibody levels.
On the other hand of the spectrum is the issue of thyroglobulin elevated negative iodine scan (TENIS). Our results showed that 10 out of 58 (17.2%) patients had elevated Tg while negative for iodine scan at 6months and this reduced to 10% (10 out of 99) at 24 months. This was in keeping with the findings of Pacini et al[54] (1987) who reported 13% (17 out of 135) patients. While all patients in the group of Pacini et al had total thyroidectomy, patients in our study population were mixed and not just the subset that had total thyroidectomy. The management of these patients include neck ultrasound (with or without FNAC), or cervico-mediastinal MRI as the commonest site for recurrence are located at these sites. If the outcome is negative, a CT scan of the lungs should be done to exclude micronodular lung metastasis. A negative finding in the lungs turns the attention to the bones for bony secondaries which should be excluded either by ^{99m}Tc MDP bone scintigraphy or another imaging agent like ^{99m}Tc MIBI , ^{201}Thallium or ^{99m}Tc Tetrofosmin . In the absence of any positive finding in all of the above the patient should have a [^{18}F] fluorodeoxyglucose positron emission tomography scintigraphic imaging to exclude potentially operative disease.[35]
Baring the 10 patients with TENIS, it seems appropriate to follow the new pattern of follow-up in which diagnostic whole body iodine-131 scan (2-5mCi) is waived for the category of patients with negative whole body iodine scan at 6 months or at the period it coincides with undetectable Tg. These patients are stabilized on T_4 therapy.

There was metastasis in 5 patients in this study. Three of the patients were below 40 years in age and the youngest was 16 years, while the remaining two patients were above 40 years, the oldest being 63 years old. Metastasis have been said to be common at the extremes of life, before age 20 and after age 60 years.[9, 22, 23] Children however commonly present with more advanced disease than adults and have more tumour recurrences after therapy but with good prognosis for survival.[23] This seems to fit with findings in this study too.

The role of laboratory back-up in the follow-up of patients treated for differentiated thyroid cancer cannot be overemphasized. The same can also be said for appropriate preparation of the patients. Adequate preparation of patients for Tg estimation with or without diagnostic scan for TSH elevation could be done by T_4 withdrawal or by the rhTSH method. TSH below 30mU/L means there is no adequate stimulation of remnant thyroid tissue or microscopic cancer. An undetectable Tg at this point is a false negative finding. Introduction of rhTSH into the protocol obviates the need for T_4 withdrawal with its attendant unpleasant effects. An undetectable Tg obtained this way is more specific. It is therefore important to have a very sensitive and reproducible Tg assay from a reliable laboratory.

In this study, several records of TSH, iodine dose and Tg were not available. The same applies to detail of surgical procedure and findings at surgery. Occasionally TSH level was not appropriately raised. The omissions can be reduced in part by computerization of records which leaves little room for omission of details often left out inadvertently by consulting physicians. Secondly computerization files the patients' laboratory results directly to the folder and this makes follow-up more objective and standardized.

The rate of default in this study was also very high. Out of 287 patients seen within the period under review, only 106 patients had the classic 2 years follow-up after being negative from a diagnostic iodine-131 scan. The majority (130) of the remaining 181 patients had incomplete records with many months of follow-up skipped, while some other patients were transferred to other facilities. Of the remaining 50 patients, 30 still had positive iodine scans while the rest have less than 2 years of negative whole body iodine scan. One may speculate what the overall result may look like if more patients have qualified for inclusion. More of the patients would have had further iodine treatment and become negative. The number of patients with TENIS would probably be more and certainly there would have been cases of patients who might have died as a result of thyroid cancer complication and or co- morbid condition.

Chapter 7: Conclusion

The main aim of this retrospective study was to find what would be the adequate follow up period and the modality for the follow-up. This study has shown that the minimum period of follow-up post becoming iodine scan negative is 24 months. Most of the patients with a negative whole body iodine scan at 6months remained with a negative scan up to this period. The same could be said for the patients that had up to 60 months of follow-up but the added period did not change their management.

The modality of follow up during the first 24 months post surgery should therefore remain based on TSH and Tg monitoring combined with a whole body iodine scan.

Finally, our data suggested that in patients with appropriately undetectable Tg and negative whole body iodine scan up to 24 months of follow up, iodine scan may not be indicated in further management of such patients. Patients should be monitored with the use of serum Tg level. If Tg becomes elevated, iodine WBS could be reinstituted together with neck ultrasonography and other relevant investigations.

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